

IMPLANT AND COATING TO REDUCE OSTEOLYSIS

BACKGROUND

[0001] The American Academy of Orthopedic Surgeons has projected annual volumes of primary total hip joint replacement to increase over 748,000 in USA or 4 million worldwide by 2030. By 2030, total hip replacement surgery is expected to rise by 174% and total knee replacement by 673%. Despite technological advances and improvements in treatment strategies to manage rheumatoid arthritis and osteoarthritis, total joint replacement (“TJR”) still remains the final treatment option in many cases to relieve pain, and improve the quality of life. Annual hospital costs associated with these procedures are projected to exceed 65 billion by 2015. However, due to osteolysis 10-15% TJR will fail, with some studies suggesting rates of osteolysis can approach 40%.

[0002] In the USA, the annual cost of TJR exceeds \$10 billion. Although joint replacement surgery has made remarkable progress, 10-15% arthroplasty failure still occurs due to high levels of free radicals, chronic inflammation and osteolysis. In 2000, 28,000 and 31,000 revision surgeries were performed for total hip arthroplasty and total knee arthroplasty, respectively and the numbers of revision surgeries are increasing each year. Revision surgeries are 40% more costly than primary total hip and knee arthroplasties and more than 1 billion dollars are spent on revision surgeries each year alone in USA. At this time, there is no drug or treatment strategies specifically approved for prevention or inhibition of periprosthetic osteolysis (hereinafter “osteolysis”).

[0003] Cerium is a rare-earth element with fluorite lattice structure with +3/+4 oxidation states and may interchange between the two depending on the environment. Cerium oxide nanoparticles (hereinafter “CNP”)s have been shown to possess a substantial oxygen storage capacity via the interchangeable surface reduction and oxidation of cerium atoms, cycling between the Ce^{4+} and Ce^{3+} redox states. CNPs have a mixed oxidation state of cerium containing both Ce^{3+} and Ce^{4+} . It has been shown that upon incubation of CNPs with hydrogen peroxide, CNPs with a higher starting concentration of Ce^{3+} can convert to CNPs containing increased Ce^{4+} on their surface. Along with this change in oxidation state is the loss of their SOD mimetic ability. However, increased Ce^{4+} on the CNP surface exhibit better catalase mimetic and .NO scavenging capabilities.

[0004] It has been well established in many studies that depending on their reactivity and surface chemistry, CNPs can effectively convert both reactive oxygen species (ROS) (superoxide, $O_2^{\cdot-}$, and hydrogen peroxide) into more inert species and scavenge reactive nitrogen species (RNS)(nitric oxide, .NO), both in vitro and in vivo. It has been further shown that CNPs significantly accelerate the decay of $ONOO^-$ and that CNPs ability to interact with $ONOO^-$ is independent of the Ce^{3+}/Ce^{4+} ratio on the surface of the CNPs.

[0005] Due to these capabilities, these materials have been employed for industrial use in three-way catalysts. Biological uses of CNPs have centered on their ability to scavenge free radicals under physiologically relevant conditions. This catalytic nature, which began with the discovery that water-based CNPs (with increased Ce^{3+} in their outer surface)

could act as superoxide dismutase mimetics, has laid the foundation for their application in experimental and biomedical research.

[0006] CNPs are known for their regenerative antioxidant activity in a biological environment. The unique regenerative property of CNPs is due to low reduction potential and the existence of both Ce^{3+}/Ce^{4+} oxidation states. It has been shown that the oxygen vacancies could act as catalytically active hot spots to scavenge very reactive radicals such as superoxide radical anion, hydrogen peroxide, nitric oxide or peroxyxynitrite. It has been shown that NC with higher levels of cerium in the +3 oxidation state exhibit superoxide dismutase activity and that this reactivity correlates with the level of cerium in the +3 oxidation state in a reversible manner. Likewise, NC with higher levels of surface cerium in the +4 oxidation state exhibit better catalase mimetic activity that also is reduced when higher levels of cerium are present in the +3 oxidation state.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] FIG. 1 is a schematic showing the mechanisms by which a NC coating can prevent osteolysis by scavenging free radicals, suppressing immune reaction locally and inhibiting corrosion, in accordance with an embodiment.

[0008] FIG. 2 shows topology and catalytic properties of the NC coating. (A) Surface morphology of EPD coated NC (left—pulse EPD; right—direct current) in accordance with an embodiment; (B) Real time degradation of H_2O_2 followed absorbance at 240 nm; (C) ROS estimated using H_2DCF fluorescence in an NC coated substrate in accordance with an embodiment; and (D) RNS using APF fluorescence assay in an NC coated substrate, in accordance with an embodiment.

[0009] FIG. 3 shows (A) HRTEM images of NC1. 3-5 nm NC1; (B) the interplanar spacing of lattice, representation of fluorite structure of NC (selected area diffraction pattern). (C) XPS spectra show variation in Ce^{3+}/Ce^{4+} in two different NC (solid line NC1; sphere—NC2).

[0010] FIG. 4 depicts RAW cells grown for 18 hr on the surface of 3 min and 6 min EPD coated Ti substrate.

[0011] FIG. 5 shows matrix metalloproteinases, MMP9, MMP12 and MMP14 expression in a nanocerium coated substrate after induction with RANKL OR TNF.

[0012] FIG. 6 shows a measure of cell proliferation on a coated Ti-metal substrate at different roughnesses, in accordance with an embodiment.

[0013] FIG. 7 shows primary human osteoblasts were plated onto type I collagen-coated (A) control or (B) NC-coated Ti plates & cultured for 8 days. Alkaline phosphatase activity was visualized by Vector Red staining, in accordance with an embodiment.

[0014] FIG. 8A shows an electric field simulation in a two v. three electrode configuration.

[0015] FIG. 8B is a graph showing the coating Ce^{3+}/Ce^{4+} ratio as a function of electrode distance and time, in accordance with an embodiment.

[0016] FIG. 9 are photos showing a comparison showing RAW cell growth on EPD coated Ti-substrate and a control Ti (uncoated).

[0017] FIG. 10 is a graph showing NFkB-LUC Activity in RAW osteoclast progenitors (TK *Renilla* Normalized).

[0018] FIG. 11A shows the intensity of the electric field of the electrodes obtained by finite element modeling using COMSOL.